REMARKS

In the application, Claims 1-48 are pending, all claims have been rejected. Claims 1-18, 25 and 43 have been amended to more precisely claim the present invention.

Rejection under 35 USC §112, 1st paragraph

The Examiner rejected Claims 1-17 and 43-48 under 35 USC §112, 1st paragraph, as allegedly not conveying that the inventors, at the time of filing, had possession of the claimed invention.

The inventive specification on page 12, line 13 through page 18, line 21 describes at least one implementation of the inventive processing module, showing possession of the invention by the Applicants at the time of filing. This realization of the processing module includes the following algorithms, applied sequentially:

A.1 Image Deconvolution and Segmentation Algorithms, Claims 1 and 3

This portion of the specification on page 12, line 13 to page 13, line 26, describes three separate algorithms to accomplish deconvolution and segmentation:

Application of a known median filter, (see reference to Tukey (1971)), used to reduce "shot noise" in the image due to photo multiplier noise during image collection is described on page 12, line 27 to page 13, line 2.

The inventive implementation utilizes the known deconvolution algorithm by Kawata and Ichioka (1980), described on page 13, lines 3-10, amended by a non-negativity constraint described on page 13, line 11. As stated on page 12, lines 15-26, deconvolution methods for optical microscopy images require either measured or theoretically approximated point spread functions (PSF). A measured PSF is used as described on page 13, lines 12-17. Figures 1(a-c) provide explicit evidence of the capability of the deconvolution algorithm step in the inventive module.

Description of the application of the prior art segmentation algorithm, of which there are a number available, is stated on page 13, lines 18-26, (see reference to Pal and Pal (1993)).

A2. Dendritic Backbone Extraction Algorithms, Claims 1 and 4

As described page 13, line 27 to page 14 , line 27 the dendritic backbone extraction consists of three separate algorithms.

1. An application of a prior art medial axis algorithm to obtain the skeleton of the neuron (see page 13, line 28 to page 14, line 2). An explicit reference is made to the algorithm of Lee et al. (1994) used in the inventive module.
2. The removal of disconnected components and trimming of short spurs and loops in the medial axis by Applicants' existing module is described on page 14, lines 17-21.
3. Derivation of the final backbone structure and elimination of long spurs is described on page 14, lines 23-27.
4. Algorithms two and three, used in the dendritic backbone extraction, are motivated by a discussion on page 14, lines 3-16.

Figures 2 (a-b) give explicit results of the application of the sequence of these dendritic backbone extraction algorithms in the inventive module.

A.3 Spine detection algorithms, Claims 1 and 5-8

Spine detection algorithms consisting of four steps are described on page 14, line 28 to page 18, line 2, more specifically:

1. Detached spine component detection — page 15, line 3 to 11,
2. Attached spine component detection — page 15, line 12 to page 17, line 6,
3. Component elimination — page 17, lines 7 to 16, and
4. Component merging — page 17, line 17 to page 18, line 2.

Figures 3 and 4 graphically clarify the text descriptions of implementation of steps 2 and 4 in the inventive module.

A.5 Morphological Characterization, Claims 1 and 9-17

One implementation of the analyzing module in the inventors' possession at time of filing is described on page 12, lines 9-12 and in detail on page 18, line 22 to page 20, line 2. This section contains an exact description of morphological measures performed by the inventive analyzing module. A description of the method employed to perform these morphological measures is also described.

Finally, referring to Claims 1 and 2, Examples 2 and 3, described on page 21, line 32 to page 25, line 25 (see also Tables 2-6, and Figures 5-7) demonstrate the capability of the inventive processing and analyzing modules on data prepared as described in Example 1, page 21, line 13-29.

The support for the claimed "repeating said processing steps" element is found on page 18, lines 3 to 21, and in Example 4, page 25, line 27 - page 26, line 32 and Figures 8 through 10. Page 18, lines 3 to 21, describe implementation of the image registration and spine tracing algorithms in the inventive module. Example 4 demonstrates the repeated application of the inventive processing and analyzing module to a data set consisting of 50 images. It would be obvious to those skilled in the art that repeated application of the inventive module to a time-series of related images also applies to an application of a plurality of non-related images.

It is therefore submitted that for the reasons outlined above, Claims 1-17 and Claims 43-48 are enabled by the specification. For that reason it is respectfully requested that rejection under 35 USC §112, 1st paragraph be withdrawn.

Rejection under 35 USC §112, 2nd paragraph

The Examiner rejected Claims 18-48 under 35 USC §112, 2nd paragraph as being indefinite. Specifically, the Examiner singles out the step of "comparing the at least one characteristic to a corresponding at least one characteristic of a control neuron, thereby determining the effect of a substance on a neuron" recited in Claim 18, as implying a criteria/threshold value at which a substance is having an effect. The Examiner further provides an example of comparing the same neuronal structure between control and subject neurons.

The Examiner's example, however, is not viable, as it assumes that only single values for structure measurements emerge from the results when in fact statistical measures, i.e., (distributions of values) result. It is the **distributions of values** obtained for the control and subject neurons that are to be compared, and are in fact comparable by prior art statistical inference tests.

Nevertheless, Claim 18 has been amended to recite "utilizing statistical inference tests to compare the at least one characteristic from the population of neuron structures to a

corresponding at least one characteristic from a population of corresponding structures of a control neuron, thereby determining the effect of a substance on a neuron".

With regard to clarification of the metes and bounds of the claim, the measured results recited in the claims are statistical. This is implied by the data presented in all tables and relevant Figures in Examples 2 through 7 of the specification. It is further implied by the persistent use of the word "plurality", e.g., of images, of dendrites, of spines, etc., throughout the claims. It is noted that it is standard practice in the field to consider any set of measured values as a particular finite sized realization of a true distribution and to use prior art statistical inference methods to compare measured sets of values. These inference methods provide standard thresholding criteria, e.g., alpha = 0.05, well known to those skilled in the art.

For these reasons it is respectfully requested that rejection under 35 USC §112, 2nd paragraph be withdrawn.

Rejection under 35 USC §102 (b)

The Examiner further rejected Claims 1-9 and 14-17 under 35 USC §102 (b) as being anticipated by a 1997 article in the Journal of Neuroscience, by Josef Spacek and Kristen Harris (Spacek).

In response, Spacek produces a 3D stack of image slices using the scanning electron microscopy (SEM) imaging method. The SEM imaging method places limitations on what techniques are developed by Spacek. Dendrites are not analyzed in Spacek as dendrites are much too large a structure to be fully viewed by SEM. Consequently Spacek concentrated on fine structures, such as dendritic spines, synaptic junctions, and the interior components of these.

In Spacek, personal computer-based (PC-based) computer aided drawing/design (CAD) software is used, each slice is displayed on a computer screen and the user **manually traces** structures of interest using the computer mouse cursor on the screen. Once the closed outline of any structure has been traced, the software automatically computes areas of the structure in each slice. By knowing slice thickness, this can be converted to a volume measurement across slices. Dendritic spines are subjectively classified using visual comparison of length and neck and head

diameters. No techniques for analyzing time series data have been developed by Spacek since the SEM imaging method requires the killing, preserving, and physical slicing, of tissue.

The present invention as claimed in independent Claims 1, 18, and 43 identifies dendrites and spines and their outlines by algorithmically tracing them without any human interaction. Spine length and head and neck diameter measurements and spine classification are all done algorithmically without human interaction. In time series images, entire three dimensional (3D) volumes have to be positionally registered with each other in order to identify the same spine all the way through the time series. Since Spacek cannot do time series, such registration does not enter into their technique. The present invention automatically registers consecutive three dimensional time series images with each other, as claimed in independent Claims 1, 18 and 43.

It can thus be seen, for at least that reason, that Spacek does not teach or describe the recitations of independent Claims 1, 18 and 43. It is thus respectfully requested that the rejection under 35 USC §102(b) be withdrawn and Claims 1, 18 and 43 as amended be allowed.

Without conceding the patentability per se of dependent Claims 2-17, 19-42, and 44-48 it is respectfully submitted that they are allowable by virtue of their dependences on independent Claims 1, 18, and 43.

Applicants respectfully submit that all of the claims of the application as presented herein, are in condition for allowance. An early and favorable action is earnestly solicited.

Respectfully submitted,

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